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Original article

Clinical characteristics and outcomes of dilated phase of hypertrophic cardiomyopathy: Report from the registry data in Japan

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ABSTRACT

Background: A subset of patients with hypertrophic cardiomyopathy (HCM) has been reported to progress into dilated-HCM (D-HCM), characterized by left ventricular (LV) systolic dysfunction and cavity dilatation, resembling idiopathic dilated cardiomyopathy (DCM). We compared the characteristics, treatments, and outcomes in patients with heart failure (HF) due to D-HCM vs. DCM by using national registry data in Japan.

Methods and results: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) is a prospective observational study of patients hospitalized due to worsening HF with an average of 2.2 years of follow-up. Patients with D-HCM ($n = 41$) were more likely to be male, have prior stroke, atrial fibrillation, and sustained ventricular tachycardia or ventricular fibrillation compared with DCM ($n = 486$). Echocardiography demonstrated that D-HCM patients had smaller LV end-systolic diameter, higher ejection fraction, and greater wall thickness. Treatments for HF including angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, and spironolactone were similar between groups except for higher use of amiodarone, warfarin, and implantable cardioverter-defibrillator for D-HCM. Mortality was significantly higher in patients with D-HCM (29.7% vs. 14.4%; $p < 0.05$). Sudden death tended to be higher also in D-HCM (8.1% vs. 2.6%; $p = 0.06$), which, however, did not reach statistical significance.

Conclusions: HF patients with D-HCM had higher mortality risk than those with DCM. Effective management strategies are critically needed to be established for D-HCM.

Introduction

A subset of patients with hypertrophic cardiomyopathy (HCM) has been reported to progress into the dilated and/or end-stage phase, the so-called dilated phase of HCM (D-HCM), characterized by left ventricular (LV) systolic dysfunction and cavity dilatation. D-HCM has been recognized as a not rare complication with distinctively unique clinical features [1–12]. One such feature of D-HCM is unfavorable outcomes including higher risk of sudden cardiac death. Therefore, it is of critical importance to analyze the clinical characteristics, treatment strategies, and prognosis for these patients in a large, multicenter population. Harris et al. reported that, using the data of 44 patients with the end-stage phase of HCM obtained from 3 HCM cohorts composed of 1259 patients, D-HCM patients had more atrial fibrillation, impaired LV function that precedes cavity dilatation, wall thinning, and heart failure (HF) symptoms [11]. Strikingly, their prognosis was unfavorable with a mortality rate as high as 11% per year. A recent study by Hamada et al. also demonstrated that patients with D-HCM were more symptomatic at diagnosis and their prognosis was worse than that for patients with idiopathic dilated cardiomyopathy (DCM) [12]. Even though their study provided a valuable insight into the characteristics of D-HCM patients in Japan, they were data from a single center of a university hospital. Therefore, we need to analyze the data for D-HCM patients obtained from multiple hospitals on a national basis.

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) is a national prospective registry database describing the clinical characteristics, treatments, and long-term outcomes of patients hospitalized due to the worsening of HF symptoms [13–18]. It included HF patients with D-HCM as well as DCM and thus could enable us to compare these 2 groups of patients.

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Methods

Baseline patient data

The details of the JCARE-CARD were described previously [13,14]. Briefly, eligible patients were those hospitalized due to worsening HF as the primary cause of admission. Baseline data were collected by using an electronic data capture system, which included demography, causes of HF, medical history, clinical status, echocardiography, plasma brain-type natriuretic peptide (BNP), and treatments including medications at discharge.

Diagnosis of HCM was based on echocardiographic documentation of a hypertrophied nondilated LV in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident at some time during the natural course of the disease [19]. D-HCM was defined as an LV ejection fraction (EF) <50% at rest, reflecting global systolic dysfunction, at study entry or during follow-up, by 2 dimensional echocardiography.

DCM was diagnosed by a dilated LV (end-diastolic diameter >55 mm) and reduced EF <50% in the absence of any specific cardiac or systemic diseases such as coronary artery disease, valvular heart disease, storage disease, and history of cardiotoxic drug use.

Outcomes

The status of registered patients was surveyed during hospitalization and at least 1 year after discharge and the following information was obtained: death, causes of death, and rehospitalization due to the exacerbation of HF that required more than continuation of their usual therapy on prior admission. Out of 527 registered patients, the follow-up data could be obtained in 455 patients (86.3%; 37 and 418 for D-HCM and DCM, respectively). Mean post-discharge follow-up was 815 ± 299 days (2.2 ± 0.8 years).

Statistical analysis

Patient characteristics and treatments were compared using Pearson χ^2 test for categorical variables, Student *t*-test for normally distributed continuous variables, and Mann–Whitney *U* test for continuous variables not normally distributed. Kaplan–Meier method was applied to all cause-death, cardiac death, sudden death, and rehospitalization due to worsening HF after discharge. A Cox proportional hazard model was used in the analysis adjusted for the following covariates: age, sex, diabetes mellitus, prior stroke, atrial fibrillation, sustained ventricular tachycardia and/or fibrillation, heart rate, diastolic blood pressure, LVEF, wall thickness of interventricular septum and posterior wall. SPSS version 16.0 J was used for all statistical analyses, and $p < 0.05$ was considered significant.

Results

Patient characteristics

Table 1 compares the baseline clinical characteristics among patients with D-HCM ($n = 41$) and DCM ($n = 486$). Compared with

Table 1
Baseline characteristics of HF patients with D-HCM vs. DCM.

Characteristics	Total ($n = 527$)	D-HCM ($n = 41$)	DCM ($n = 486$)	*p*-Value
Age, yrs (mean ± SD)	63.5 ± 13.9	63.6 ± 14.3	63.5 ± 13.8	0.963
Male, %	73.1	87.8	71.8	0.027
BMI, kg/m^2	22.6 ± 4.1	23.3 ± 3.2	22.5 ± 4.2	0.132
Duration of HF, months (mean ± SD)	47.5 ± 63.2	39.5 ± 32.6	48.1 ± 65.0	0.236
Medical history, %				
Hypertension	31.7	24.4	32.4	0.292
Diabetes mellitus	23.9	0.0	25.9	<0.001
Dyslipidemia	20.8	26.8	20.2	0.318
Hyperuricemia	48.3	62.5	47.2	0.062
COPD	6.0	2.5	6.3	0.330
Smoking	43.7	33.3	44.4	0.214
Prior stroke	10.3	23.7	9.3	0.005
Prior myocardial infarction	3.3	7.3	2.9	0.128
Atrial fibrillation	33.7	51.2	32.2	0.014
Sustained VT/VF	8.5	23.1	7.3	0.001
Vital signs at discharge				
NYHA functional class, %				
1	32.7	26.8	33.2	0.844
2	57	63.4	56.4	
3	7.5	7.3	7.5	
4	2.9	2.4	2.9	
Heart rate, bpm	71.1 ± 12.3	66.0 ± 10.6	71.5 ± 12.4	0.015
SBP, mmHg	110.2 ± 17.2	105.0 ± 23.2	110.6 ± 16.6	0.14
DBP, mmHg	65.2 ± 11.4	60.3 ± 13.7	65.6 ± 11.1	0.007
Laboratory data at discharge				
eGFR, mL/min/1.73 m^2	56.6 ± 23.7	53.1 ± 25.9	56.9 ± 23.5	0.121
Serum uric acid (mg/dL)	7.4 ± 2.3	7.8 ± 2.4	7.4 ± 2.3	0.318
Hemoglobin, g/dL	13.2 ± 2.2	13.7 ± 1.9	13.1 ± 2.2	0.203
Plasma BNP, pg/mL	370 ± 438	450 ± 391	365 ± 411	0.154
Echocardiographic data				
LV EDD, mm	64.0 ± 8.5	60.3 ± 13.7	65.6 ± 11.1	0.127
LV ESD, mm	64.0 ± 8.5	50.3 ± 7.9	55.0 ± 9.4	0.003
LVEF, %	29.4 ± 11.2	34.4 ± 11.5	29.0 ± 11.0	0.005
IVST, mm	9.6 ± 2.3	11.7 ± 3.6	9.4 ± 2.1	<0.001
LV PWT, mm	9.6 ± 2.0	10.8 ± 2.9	9.5 ± 1.9	0.004
Severe mitral regurgitation, %	30.6	26.5	30.9	0.586

D-HCM, dilated phase hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; BMI, body mass index; HF, heart failure; COPD, chronic obstructive pulmonary disease; VT/VF, ventricular tachycardia/fibrillation; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EF, ejection fraction; IVST, interventricular septal thickness; PWT; posterior wall thickness. Data are shown as percent or means ± SD.

patients with DCM, the patients with D-HCM were more male and more likely to have a history of stroke, atrial fibrillation, and sustained ventricular tachycardia and/or fibrillation.

New York Heart Association functional class at discharge was comparable between groups. Plasma BNP levels were elevated in both D-HCM and DCM patients, but they did not differ between groups (450 ± 391 pg/mL vs. 365 ± 411 pg/mL; $p = 0.154$). Echocardiographic data showed that LV cavity diameters were increased and EF was decreased in both groups. However, compared to DCM, LV end-systolic diameter was smaller (50.3 ± 7.9 mm vs. 55.0 ± 9.4 mm; $p = 0.003$) and EF was greater (34.4 ± 11.5% vs. 29.0 ± 11.0%; $p = 0.005$) in patients with D-HCM. As expected, the wall thickness of interventricular septum and posterior wall was greater in D-HCM than in DCM. The prevalence of severe mitral regurgitation was comparable between groups.

Treatments

Table 2 compares the medication and procedure use at the time of discharge. The majority of both D-HCM and DCM patients were treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs; 80–90%) and β-blocker (approximately 73%), which did not differ between groups. The use of spironolactone was also comparable between groups (42.5% vs. 46.9%, $p = 0.592$). In contrast, the use of antiarrhythmics including amiodarone was significantly higher in patients with D-HCM (30.0% vs. 15.4%, $p = 0.017$). Implantable cardioverter-defibrillator (ICD) use was also higher in D-HCM compared to DCM (20.0% vs. 2.8%, $p < 0.001$). The use of warfarin was higher in D-HCM compared to DCM (77.5% vs. 49.9%, $p = 0.001$).

Long-term outcomes

During the follow-up period, 29.7% of D-HCM patients died, which was significantly higher than the 14.4% for DCM patients ($p < 0.05$) (Fig. 1). The rate of cardiac death (21.6% vs. 9.8%; $p = 0.08$) and sudden death (8.1% vs. 2.6%; $p = 0.06$) tended to be higher in D-HCM than DCM, which, however, did not reach statistical significance. The rate of rehospitalization during the same period tended to be higher in patients with D-HCM than DCM, which was not statistically significant (43.2% vs. 31.8%, $p = 0.102$).

After adjustment for covariates in multivariate Cox proportional hazard models, patients with D-HCM were not significantly associated with higher risk of all-cause death [hazard ratio (HR) 1.832, 95% confidence interval (CI) 0.775–4.329, $p = 0.168$], cardiac death (HR 2.219, 95% CI 0.726–6.777, $p = 0.162$), sudden death (HR 0.725, 95% CI 0.058–9.098, $p = 0.803$), and rehospitalization due to worsening HF (HR 1.174, 95% CI 0.578–2.385, $p = 0.657$) compared to those with DCM (Table 3).

Deletion of 3 D-HCM patients and 14 DCM patients with prior myocardial infarction did not affect the overall results. The rate of all-cause death in D-HCM patients without prior myocardial infarction was significantly higher than that for DCM patients (HR 2.128, 95% CI 1.088–4.165, $p = 0.024$). The rate of cardiac death (HR 2.14, 95% CI 0.959–4.776, $p = 0.057$) and sudden death (HR 3.393, 95% CI 0.946–12.166, $p = 0.046$) tended to be higher in D-HCM than DCM without prior myocardial infarction, which, however, did not reach statistical significance. They did not significantly differ between groups after adjustment for covariates in multivariate Cox proportional hazard models.

Discussion

The present study based on the JCARE-CARD provides a comparison of the clinical characteristics, treatments, and outcomes of HF patients due to D-HCM vs. DCM in routine clinical practice in Japan. It confirmed previous studies that D-HCM patients had more atrial fibrillation, sustained ventricular tachycardia and/or fibrillation, and poor prognosis [11,12].

The number of D-HCM ($n = 41$) was smaller than those of DCM ($n = 486$) in this study. Prevalence of HCM is about 0.2% in general population and about 3% of HCM patients manifest the end stage characterized by systolic dysfunction (LVEF <50%) [11,20]. Consequently, the prevalence of D-HCM was estimated as 0.006%. On the other hand, the prevalence of DCM has been reported to be approximately 0.036% in the general population [21]. The ratio of D-HCM to DCM is estimated to be 1–6 in the general population. The ratio in this study (1–12) might be lower than the estimated value in general population, which might be due to the selection bias of the

Table 2
Discharge medications and procedures for HF Patients with D-HCM vs. DCM.

	Total ($n = 527$)	D-HCM ($n = 41$)	DCM ($n = 486$)	p-Value
Medications, %				
ACE inhibitor	48.9	42.5	49.5	0.397
ARB	47.0	45.0	47.1	0.796
ACE inhibitor or ARB	88.4	80.0	89.1	0.084
ACE inhibitor and ARB	7.5	7.5	7.5	0.993
β-Blocker	73.9	72.5	74.0	0.837
Diuretics	90.0	97.5	89.3	0.099
Loop diuretics	79.2	80.0	79.1	0.893
Spironolactone	46.6	42.5	46.9	0.592
Digitalis	39.1	35.0	39.4	0.580
Ca channel blocker	11.8	15.0	11.5	0.512
Nitrates	11.4	12.5	11.3	0.819
Antiarrhythmics	26.1	47.5	24.3	0.001
Amiodarone	16.5	30.0	15.4	0.017
Aspirin	28.3	25.0	28.6	0.630
Warfarin	52.1	77.5	49.9	0.001
Statin	14.3	17.5	14.1	0.553
Procedures, %				
PCI	5.1	9.8	4.8	0.164
Valvular surgery	1.0	0.0	1.0	0.513
PPM	0.8	2.4	0.6	0.197
ICD	4.1	20.0	2.8	<0.001
CRT	4.7	7.5	4.5	0.387

D-HCM, dilated hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.

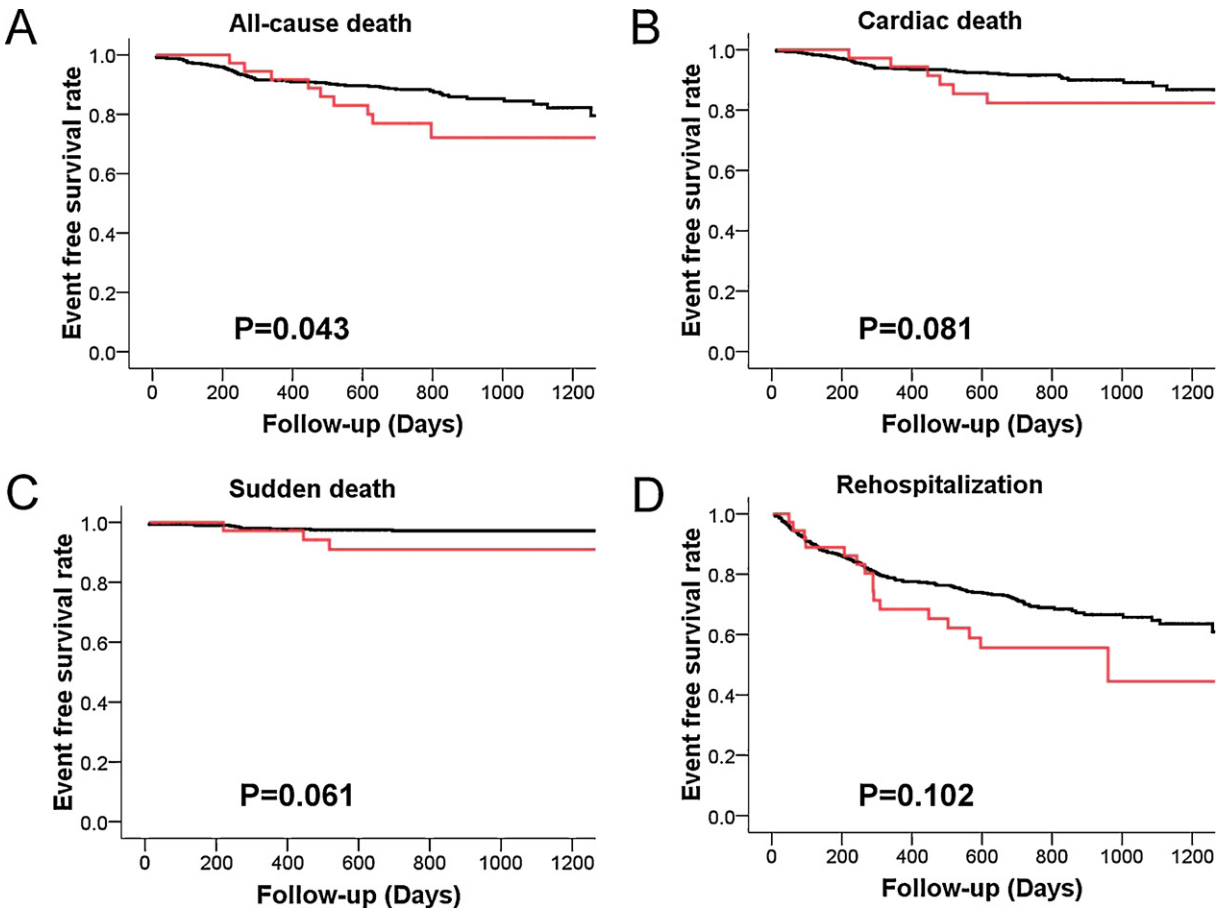

Fig. 1. Unadjusted Kaplan–Meier survival curves free from (A) all-cause death, (B) cardiac death, (C) sudden death, and (D) rehospitalization due to heart failure in patients with dilated hypertrophic cardiomyopathy (red lines; $n = 37$) compared with dilated cardiomyopathy (black lines; $n = 418$).

Table 3
Unadjusted and adjusted hazard ratios for outcomes in HF patients with D-HCM ($n = 37$) compared with DCM ($n = 418$).

Outcomes	Number (%)		HR	95% CI	p-Value
	D-HCM ($n = 37$)	DCM ($n = 418$)			
All-cause death	11 (29.7%)	60 (14.4%)			
Unadjusted			1.969	1.007–3.850	0.043
Adjusted for covariates			1.832	0.775–4.329	0.168
Cardiac death	8 (21.6%)	41 (9.8%)			
Unadjusted			2.013	0.902–4.491	0.081
Adjusted for covariates			2.219	0.726–6.777	0.162
Sudden death	3 (8.1%)	11 (2.6%)			
Unadjusted			3.181	0.887–11.407	0.061
Adjusted for covariates			0.725	0.058–9.098	0.803
Rehospitalization	16 (43.2%)	133 (31.8%)			
Unadjusted			1.542	0.917–2.592	0.102
Adjusted for covariates			1.174	0.578–2.385	0.657

The Cox proportional hazard model was used in the analysis adjusted for the following covariates: age, sex, diabetes mellitus, prior stroke, atrial fibrillation, ventricular tachycardia/fibrillation, heart rate, diastolic blood pressure, left ventricular ejection fraction, interventricular septal thickness, and left ventricular posterior wall thickness. Patients with DCM were a reference group. D-HCM, dilated phase hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; HF, heart failure; HR, hazard ratio; CI, confidence interval.

study patients limiting those hospitalized with worsening HF and the difficulty to diagnose D-HCM in the later phase of this disease.

HCM is a heterogenous myocardial disease with a broad spectrum of clinical and morphological presentation [20]. LV systolic function is supernormal or normal in most patients with HCM. However, 3–5% of patients have been shown to progress into LV systolic dysfunction when followed for a long period [9–11]. This type of HCM is usually associated with LV wall thinning and cavity dilatation, resembling the morphologic features of idiopathic DCM and is thus called “the dilated phase of HCM”. However, in contrast to DCM, there have been several clinical features reported in patients with D-HCM; higher incidence of ventricular tachycardia/fibrillation and the resultant poor prognosis [12].

The clinical features of D-HCM in the present study were similar to those of the previous studies [11,12]. HF patients with D-HCM were more often male, and more likely to have atrial fibrillation and sustained ventricular tachycardia/fibrillation (Table 1). A recent study by Melacini demonstrated that atrial fibrillation was noted in 64% of patients with HCM complicated by progressive HF and was identified as the single most important factor in HF evolution [22].

Atrial fibrillation was also related to left atrium size and impaired LV diastolic function in patients with HCM [23]. These findings are consistent with previous studies that the combination of atrial fibrillation is particularly adverse in patients with HCM [24]. Higher prevalence of atrial fibrillation (Table 1) might be also associated with higher rate of prior stroke in patients with D-HCM (Table 2).

The present study demonstrated that D-HCM patients in our Japanese registry received the guideline-recommended medical treatment for HF with reduced EF including ACE inhibitors, ARBs, β-blockers, and spironolactone (Table 2) [25,26]. The use of these medications was similar to that for patients with DCM in our study cohort. An important difference was higher use of amiodarone and ICD implantation in the D-HCM group (Table 2), which was in parallel to high prevalence of sustained ventricular tachycardia/fibrillation (Table 1). ICD implantation should be considered for patients with D-HCM based on the finding that sustained or nonsustained ventricular tachycardia is commonly seen and sudden cardiac death frequently occurs in these patients [27]. Cardiac resynchronization therapy is also needed for patients with D-HCM and wide QRS because it has been shown to improve the symptoms and produce reverse LV remodeling also in this type of patient [28]. In parallel to higher prevalence of atrial fibrillation in patients with D-HCM (Table 1), the use of warfarin was significantly higher in this group (Table 2).

During the long-term follow-up, the mortality rates in patients with D-HCM were higher than those with DCM (Fig. 1). These results are also consistent with previous studies [11,12]. Harris et al. demonstrated that the mortality rate was as high as 11% per year and sudden death including ICD intervention was prevalent (34% of total death) in patients with the end-stage phase of HCM [11]. Similarly, Hamada et al. reported that the 5-year survival rate free from all-cause death including cardiac transplantation was lower in patients with D-HCM than in DCM (45.6% vs. 81.6%; $p = 0.0001$) [12]. Poor survival might be also due to the progressive myocyte loss, fibrosis, and the resultant LV wall scarring/thinning in patients with D-HCM [29]. Recently, it has been also reported that extracellular matrix protein and proteinase are related to LV remodeling and prognosis in patients with HCM [30,31]. Supporting evidence for this hypothesis is the higher prevalence of ventricular tachycardia in these patients. Although the present study suggested a higher rate of cardiac death and sudden death in D-HCM, this difference did not reach statistical significance in our studied patients, which might be due to relatively high use of treatments known to be effective for the prevention of sudden cardiac death such as β-blockers and amiodarone as well as ICD (Table 2). Despite the risk for long-term adverse outcomes, sufficient data are lacking to prove the effective treatment strategies for HF patients with D-HCM. Current HF guideline recommendations include use of ACE inhibitors and β-blockers, for patients with reduced EF due to either DCM or D-HCM [25,26]. Given the high post-discharge clinical event rate and the lack of proven medical therapies for this type of HF, there is a clear need to establish effective management strategies.

There are several limitations which should be acknowledged in the present study. First, the present observations included only hospitalized patients with worsening HF, a population known to be at increased risk of adverse outcomes including mortality and rehospitalization. However, by using the criteria regarding their symptoms and signs sufficiently severe to be hospitalized for HF, we could enroll patients with reasonably uniform status on admission. Second, it is difficult to diagnose D-HCM in the late phase of HCM. The diagnosis of HCM was judged by cardiologists that participated in this study with clinical records and the definition of D-HCM in this study was previous or current diagnosis of HCM with reduced EF by echocardiography. To accurately diagnose D-HCM, we need more precise information about the diagnosis of HCM, but it is difficult from our national prospective registry database. Third, data before progressing into D-HCM were not obtained in the present study and thus we could not include these variables in the analysis. However, the purpose of this study was to compare the clinical characteristics and outcomes of D-HCM with those of DCM among patients hospitalized due to worsening HF. To clarify the characteristics and outcomes of D-HCM, we need to establish a prospective cohort of HCM patients with much longer follow-up. Fourth, the data were dependent on the accuracy of documentation and abstraction by individual hospitals and cardiologists that participated in this study. However, it is not the objective of this survey to restrict enrollment to the narrowly defined patient population of D-HCM. Fifth, we did not collect data on family history because this study intended to analyze HF patients due to various causes, and was not limited to HCM or DCM. Finally, we did not have the detailed information regarding the causes of death in our study patients. Further studies focusing on this crucial issue are clearly needed in patients with D-HCM vs. DCM.

In conclusion, D-HCM was present in a certain proportion of hospitalized patients with worsening HF in the large unselected registry in Japan. Although D-HCM resembles DCM in terms of LV systolic dysfunction and cavity dilatation, patients with HF and D-HCM differ significantly from those with DCM, especially with a higher rate of mortality. Given the high risk of adverse clinical events and the lack of a sufficient evidence to guide the treatment, clinical trials are needed to identify effective management strategies for D-HCM.

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